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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,480	08/13/2002	Robert Heger	49619	4809

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EXAMINER
YOUNG, MICAH PAUL

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
06/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/857,480	HEGER ET AL.	
	Examiner	Art Unit	
	Micah-Paul Young	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-21 and 23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-21 and 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Papers Received: Response dated 3/14/07.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 15-18 and 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Vallet Mas, et al (EP 0 717 989 hereafter '989) in view of Redlich et al (USPN 5,225,279 hereafter '279). The claims are drawn to a method for making nanoparticles comprising spraying together a core mixture and a shell mixture forming a core/shell nanoparticle. The core mixture can comprise various acrylic or methacrylic polymers, while the shell can comprise various natural or synthetic polymers. The resulting nanoparticle is in the range of 0.05-0.9 microns.

4. The '989 patent discloses a method of making coating nanocapsules comprising a core and shell (abstract). The methods comprise spraying a mixture of a core preparation (PHASE 1)

into a separate shell preparation (PHASE 2) where the two mixtures meet at a "Y" junction in the mixing chamber (page 4, line 18-25). Phase 1 comprise solvents and non-solvents for the polymers of Phase 2, along with possible active agents, surfactants and other dispersants (page 3, lin. 12-30). The two phases are mixed within the chamber in a continuous process that provides an immediate deposition of polymer around the droplet or particle (**Ibid.**) This allows for continuous mixing and results in nanoparticles in the range from 0.2-0.5 microns (page 3, lin. 8-12). The coating polymers include acrylic acids (page 4, lin. 11-15). The reference discloses different polymers for the core however the polymers recited are hydrophobic and ideal for similarly water insoluble active agents (examples). A hydrosol is produced during the process (examples) and is eliminated. A skilled artisan would be motivated to find improved polymers in order to incorporate a wider variety of active agents. This can been in the '279 patent.

5. The '279 patent discloses core/shell particles comprising acrylate and methacrylate copolymers (abstract). The core/shell nanoparticles further include surfactants and dispersing agents (col. 5, lin. 8). The core comprising methyl methacrylate (example 1). The core/shell particles are in a range from 0.27-0.32 microns (col. 9, lin. 34-45). A skilled artisan would be motivated to include the methacrylate polymers in order to incorporate water-insoluble active agents such as isothiazolone (col. 11, lin. 55-60).

6. Regarding the phases of the core/shell it is the position of the Examiner that the core/shell nanoparticles creates would inherently comprise phases with and without drug since the cores comprise active agents in addition to polymers forming areas of drug and areas of polymer. Regarding the particle size change during the hydrolysis of the particles, it is the position of the Examiner that this limitation does not impart patentability since the ending particle sizes of the

'989 procedure meet the limitations of the claims. The core/shell particle made from the '989 patent are formed by continuously spraying a core and coating composition together in order to form nanoparticles of a particular size within the limits of the claims. The change in size of an intermediate product is irrelevant, since the end result is a nanoparticulate formulation of identical size.

7. With these aspects in mind it would have been obvious to combine the acrylic polymers of the '279 patent into the '989 process in order to incorporate a wider range of hydrophobic agents and impart acid stability on the nanoparticle formulation. One of ordinary skill in the art would have been to combine the teachings in order to provide a core/shell product with improved stability and a wider range of active agent carrying capacity.

8. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Vallet Mas et al (EP 0 717 989 hereafter '989) in view of Weitshies et al (USPN 6,068,857 hereafter '857). The claims are drawn to a method of making nanoparticles with a core/shell structure. The shell comprise gelatin.

9. As discussed above the '989 patent discloses a method of making nanoparticle formulations comprising a core/shell structure, where the core and shell formulations are sprayed into each other in a continuous mixing process. The reference teaches that natural copolymers can be used in the coating phase of the formulation. Natural polymers such as gelatin and polymeric peptides are well known coating components as can be seen in the '857 patent.

10. The '857 patent discloses a nanoparticle formulation comprising a core/shell structure (abstract). The shell phase can comprise a wide range of natural materials and their derivatives

such as gelatin, albumin, succinylated gelatin, crosslinked polypeptides, chitosan and pectin (col. 4, lin. 1-7), as well as synthetic polymers such as copolymers of lactic acid and polyesters (col. 4, lin. 8-20). A skilled artisan would be able to interchange the natural polymers of the '857 into the process of the '989 since all of the polymers are art recognized biodegradable/acceptable equivalents.

11. It would have been obvious to one of ordinary skill in the art would have been motivated to combine the natural polymers of the '857 patent as suggested by the '989 patent in order to provide stability and structural integrity to the nanoparticle formulation. Further since the polymers are art recognized equivalents of one another it would have been well within the level of skill in the art to combine the teachings with an expected result of a stable biocompatible formulation.

12. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of the Vallet Mas et al (EP 0 717 989 hereafter '989) in view of Liversidge et al (USPN 6,045,829 hereafter '829). The claims are drawn to a method of making a nanoparticle formulation with a core/shell structure where the shell casein or sodium casienate.

13. As discussed above the '989 patent discloses a method of making nanoparticle formulations comprising a core/shell structure, where the core and shell formulations are sprayed into each other in a continuous mixing process. The reference teaches that natural copolymers can be used in the coating phase of the formulation. Natural polymers such as casein are well known coating components as can be seen in the '829 patent.

14. The '829 patent discloses a nanoparticle formulation where the surface of the shell are stabilized by the inclusion of natural polymers such as gelatin, lecithin and casein (col. 7, lin. 35-37). He nanoparticles are in the range of 0.1-0.4 microns (col. 8, lin. 45-20). The process for making the particles in continuous from mixing to sieving (examples). A skilled artisan would be motivated to include the casein of the '829 patent in order to impart improved stability to the formulation.

15. It would have been obvious to combine the stabilizers of the '829 patent in to the process of the '989 patent in order to improve the surface stability of the nanoparticle formulation. One of ordinary skill in the art would have been motivated to combine the teachings with an expected result of a stabilized nanoparticle formulation with improved bioavailability and bioacceptability.

Response to Arguments

16. Applicant's arguments filed 3/14/07 have been fully considered but they are not persuasive. Applicant argues that;

a. The '989 and '279 patent do not obviate the claims since they do not disclose each and every element of the invention.

b. The '989 and 857 patents do not obviate the claims since they do not disclose each and every element of the invention.

c. The '989 and 829 patents do not obviate the claims since they do not disclose each and every limitation of the invention.

17. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

18. Regarding argument a., it remains the position of the Examiner that the combination of the '989 and '279 patents remains obviating over the instant claims. The '989 patent provides a method of making coated nanoparticles with a particle size between 0.2-0.5 microns. The coating and core solutions/emulsion are sprayed together in a jet and combined in the chamber in a continuous process. The coatings comprise acrylic acids. A hydrosol is formed during the process and removed. The reference is silent to the nature of the drug applied to the core in the examples. However since no dissolution is required in the example it is the position of the Examiner that the drug is amorphous or at least non crystalline in nature since dissolution is not required, and the core emulsion solution is not a suspension of materials. The reference discloses different specific polymers of the core, yet they are hydrophobic and ideal for water insoluble active agents, as shown in the '279 patent. The '279 patent establishes the level of skill in the art regarding the making of core/shell particles comprising methyl methacrylate polymers and active agents. The particles have an average size between 0.27-0.32 microns and comprise isothiazolone in an emulsion/solution. Again like the '989 patent, no process steps are disclosed requiring a dissolution of the drug, meaning that active ingredient is at least non-crystalline or amorphous providing an improved and eased absorption by the body. For these reasons the claims remain obviated by the art.

19. Regarding argument b., it remains the position of the Examiner that the combination of the '989 and the '857 obviates the claims. As discussed above the '989 patent discloses a process for making coated nanoparticles in a continuous process where the core and coating are

sprayed together and mixed into a chamber. The reference discloses different coating polymers, yet suggests the inclusion of natural polymers. The '857 patent establishes the level of skill in the art regarding the application of natural polymers such as gelatin to nanoparticulate formulations. It would have been obvious to include these polymers in order to improve the bioavailability of the particles upon delivery to the body. For these reasons that claims remain obviated.

20. Regarding argument c., it remains that position of the position of the Examiner that the combination of the '989 and '829 patents renders the instant claims obviated. As discussed above the '989 patent disclose a continuous method of making coated nanoparticles where the core and coating compositions are sprayed together in a continuous process a mixing in a chamber and resulting in particles within the ranges of the instant claims. Natural polymers are suggested by the reference yet the specific polymers are different. It would be well within the level of skill in the art to apply well-known natural polymers to the process of the '989 patent. The ''829 patent establishes the level of skill in the art regarding the coating of drug containing particles with natural polymers such as casein and sodium casienate. It would have been obvious to include the polymers of the '829 such as lecithin, gelatin and casein into the process of the '989. The particles of the '829 patent range in size from 0.1-0.4 microns and the process is continuous. The reference also establishes the benefit of using amorphous drugs since they have increased bioavailability and easier absorption. The artisan would have been motivated to combine these teachings and suggestions in order to improve the stability and bioavailability of the dosage forms. For these reasons the claims remain obviated by the prior art.

Conclusion

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

22. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Micah-Paul Young whose telephone number is 571-272-0608. The examiner can normally be reached on M-F 6:00-3:30 every other Monday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Micah-Paul Young
Examiner
Art Unit 1618

MP Young

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER